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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,922	BRAUN ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2008*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-28* is/are pending in the application.

4a) Of the above claim(s) *15-17,22-25 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-14,18-21,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and remarks filed 11/21/08 are acknowledged. Claims 1, 14, 26 have been amended and claim 4 has been canceled. Claims 1-3, 5-14, 18-21, 26, 27 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 11/21/08 response would be addressed to the extent that they apply to current rejection.

Non-Compliant Amendment

The amendment filed 11/21/08 is considered non-compliance because it has failed to meet the requirements of 37 CFR 1.121 or 1.4. Specifically because each claim has not been provided with a proper status identifier. Particularly, not all of the withdrawn claims have been correctly identified. Correction is required in the response to this Office action.

Election/Restrictions

Acknowledgement is made of Applicant's election of Group II, drawn to a method of eliciting a T cell response against a T cell epitope, wherein a combined administration of nucleotide sequence of interests and a protein is involved. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

As to the species election, the Office requires, identify a specific first, second, and third T cell epitope if the epitopes are different in different immunizations; and if applicable, identify a specific adjuvant. In the response, the applicant elected a single specific T cell epitope, i.e. HA antigen of the influenza virus. Accordingly, the elected

species is defined as a combination of multiple doses of a single type of protein and the nucleotide encoding such without the presence of an adjuvant.

Accordingly, Claims 15-17, 22-25, 28 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse.

Specification

The abstract of the disclosure stands objected to because it does not commence on a sheet separate from other materials of the disclosure. Correction is required. See MPEP § 608.01(b).

Priority

The applicant's argument is persuasive with regard to the prior-filed application, Application No. 60/526,517 and 60/567,771.

However, the disclosure of the prior-filed application, Application No. 60/510,086 fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Instant claims are directed to administer a nucleotide sequence of interest followed by a protein of interest at an interval from 21 to 365 days, whereas the provisional application discloses clusters of NOI administering without administering a protein. Apparently, the priority document fails to support instantly claimed invention. Accordingly, the priority date of the instant application for the subject matter under examination has been established as the filing date of the prior-filed application, Application No. 60/526,517 and 60/567,771, i.e. 12/4/2003.

Claim Objections

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 2 depends from claim 1, which recites, "wherein the time between the first administration of the first immunization and the first administration of the second immunization is from 21 to 365 days"; whereas claim 2 recites "wherein the administrations of the first and/or second immunization occur over 2 days...", which does not fall into the range provided in claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-14, 18-21, 26, 27 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited

to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are directed to a vaccine regimen for inducing a T cell response against a T cell epitope in a mammalian subject comprising DNA-prime and protein-boost regimen, wherein the claims broadly encompass any antigen of interests. Although the specification contemplates the DNA prime and protein boost regimens, and the specification provides multiple examples of various plasmid vectors encoding different types of viral antigens, it does not provide a single example of protein-boost regimen. Hence, the enablement lies on the state of the art (see prior art rejections below). Although there were numerous prior art documents inducing T cell response through DNA-priming and protein-boosting, the state of the art is such there were many variations and unknown factors for different antigens, different routes of delivery, different dosing regimen, etc. For example, see teachings of *Doria-Rose et al* (Methods 2003;31:207-16). To this end, the specification fails to teach the claimed specific regimens would apply to the genus of antigens. US patent 6,500,432 claims, for enhancing a CTL response, the polypeptide should be administered 1-10 days after the polynucleotide (see claims 1-2). It is unclear and the specification fails to teach how applicant came up with the number as recited in the claims, as opposed to the number in the claims of the '432 patent. *Rasmussen* (J Med Primatol 2002;31:40-60) reported, using DNA prime/protein boost vaccine strategy, they fail to generate a detectable or significant T cell response against HIV antigens. In view of such, the specification does not appear to provide an enabling disclosure for the full scope of the claims.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The amended claims further limit the interval of NOI administration from 1-14 days to 2-6 days. However, the specification fails to teach how the timing of 2-6 days would influence the degree of T cell activation as compared to 7-14 days. Turning to the state of the art, it was well known in the art that exposure to an antigen would activate lymphocytes to proliferate, duplicating themselves two to four times every 24 hours for 3-5 days (*Janeway et al.* Immunobiology 2001, e.g. ¶ 1-12). Accordingly, it appears the stimulation every 3-5 days would keep the T cell proliferation going, while 7-14 days are

more than sufficient for stimulating antibody production (*Janeway et al.*, figure 1.20). The longer interval (7-14 days) may not stimulate a continued T cell response as 4-6 days, but, there should not be any significant differences whether the interval of NOI administration is 6 days or 7 days. The specification compares "clustered" (0, 2, 4) administration with "pulse" (0 or 4) administration (e.g. Specification, page 79), but it does not compare "2-6 days" vs. "7-14 days" interval. The specification fails to teach why it is patentably distinct if the NOI administration is 2-6 days apart as compared to 7 days apart as applied by *Billaut-Mulot*. Accordingly, the specification fails to provide an enabling disclosure to support the full scope of the claims.

Response to Argument

Interval between NOI and protein antigen administration

In the remarks, the applicants point to numerous teachings of the specification concerning the timing of administration, such as those recited in pages 12, and the 1st paragraph of page 13 of the remark. However, these teachings discuss the cluster of NOI administration within the claimed "first immunization", they fail to address the timing between the first and second administration of the NOI and a protein.

The applicants then point to paragraph 0026, 0190, and 0110 for teachings of the NOI prime and protein boost regimen. It is noted these paragraphs as well as in paragraphs 0111-0113, the specification generally and prophetically contemplates the claimed invention, but did not even discuss the timing between the two administrations. Accordingly, the specification fails to provide an enabling disclosure for the optimized vaccine timing of the antigen genus in view of the contradictory evidence of record.

The applicant then argues that the courts have held that compliance with the enablement requirement does not turn on whether an example is disclosed. The argument has been fully considered but found not persuasive. This is because the courts have held that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson* , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001 (Fed. Cir. 1997) at 1005. With respect to working examples, the MPEP states, "WHEN CONSIDERING THE FACTORS RELATING TO A DETERMINATION OF NON-ENABLEMENT, IF ALL THE OTHER FACTORS POINT TOWARD ENABLEMENT, THEN THE ABSENCE OF WORKING EXAMPLES WILL NOT BY ITSELF RENDER THE INVENTION NON-ENABLED." "LACK OF A WORKING EXAMPLE, HOWEVER, IS A FACTOR TO BE CONSIDERED, ESPECIALLY IN A CASE INVOLVING AN UNPREDICTABLE AND UNDEVELOPED ART." (MPEP 2164.02, 03). The Office provides numerous prior art showing variations and unpredictablility in the art concerning the timing and dosing regimen for different types of antigens, it is the applicant's duty to show otherwise, either though the teaching of the specification or through other evidence. The specification fails to do so, and thus it fails to provide an enabling disclosure for what is now claimed.

The types of antigens of the primary and secondary immunization

The applicant then argues that the present DNA examples would suggest to those skilled in the art that a second immunization could be done using any suitable T cell epitope.

The argument has been fully considered but found not persuasive because the common consent in the art is that the antigen of interest in the boosting (second) administration should be the same as the first administration, not any suitable T cell epitope that differs from the first NOI. For example, as shown by *Janeway* in figure 1.20, the characteristics of the immunological memory is readily observed by comparing the antibody response of an individual to antigens A and B in a first or **primary immunization** with the response elicited in the same individual in a **secondary** or booster immunization with the same antigen(A). As shown in Fig. 1.20, the secondary antibody response to antigen A occurs after a shorter lag phase, achieves a markedly higher level, and produces antibodies of higher affinity, or higher strength of binding, for the antigen A. However, when using a different antigen B, the response is more like a new primary immunization, rather than a booster dose, and hence, the specification fails to provide evidence contrary to what was known in the art , and hence fails to provide an enabling disclosure for what is now claimed.

The applicant then cites case laws arguing routine experimentation is permissible, and the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled.

The argument has been fully considered but found not persuasive. The Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material **or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

In the instant case, the entire body of the claims is directed to using a combined nucleic acid-protein immunization regimen for eliciting a T cell response in a specified timing, but there is no disclosure by the specification regarding how any of the conditions would fair in a real world setting. Then, either the claimed embodiment was not novel, or undue experimentation is required.

Accordingly, for reasons of record and *supra*, the rejection stands.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject

matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 8, 9, 11, 14, 18-20, 26, 27 are newly rejected under 35 U.S.C. 103(a) as obvious over *Billaut-Mulot et al.* (Vaccine 2001;19:95-102), in view of *Janeway et al.* (Immunobiology c2001).

Billaut-Mulot teaches a method of eliciting a T cell response against HIV viral infection in a mammalian host, the method comprises intradermal administering a pharmaceutical composition comprising a DNA plasmid vector encoding and expressing HIV Nef for three successive times at 1 week (=7 day) intervals, followed by a boost with recombinant Nef protein intraperioneally at 14 weeks after the first injection of the DNA (§ 2.3 page 96); Wherein the Nef coding sequence is under the control of regulatory sequence CMV promoter, BGH polyadenylation signal sequence (§ 2.1); wherein the vector is in a solution of pharmaceutical acceptable carrier. *Billaut-Mulot* reports a strong CTL response was induced (see e.g. § 3.2 and figure 3). Since the method was carried out to test the efficacy of the vaccine regimen, it is an assay as recited in claims 26 and 27. *Billaut-Mulot* differs from instant claims in that the interval for administration of NOI was 7 days apart, not 6 days apart.

Janeway supplemented *Billaut-Mulot* by establishing that it was well known in the art that lymphocytes respond to antigen exposure by proliferation (activation), duplicating themselves two to four times every 24 hours for 3-5 days (e.g. ¶ 1-12). Hence, one would expect that repeated stimulation at around 6 or 7 days by multiple administration of an NOI of interest would provide a continued T cell proliferation activity at comparable levels.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Billaut-Mulot* by adjusting the timing of antigen administration according to the knowledge taught by *Janeway* depending on the need of the degree of T cell response with a reasonable expectation of success. Given the knowledge of the skilled in the art, this limitation falls within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

The applicant argues *Billaut-Mulot* has longer time frame than instantly claimed. Claims now require all administration of NOI occur between 2 and 6 days apart.

Applicant's arguments have been fully considered but they are not persuasive. As an initial matter, the specification fails to teach what differences it makes whether administrations are 6 days apart as compared to 7 days apart. Hence, in the absence of evidence to the contrary, the one day difference would be considered as a matter of optimization. Further, it was well known in the art the time needed for eliciting a T cell response as taught by *Janeway*. The skilled in the art would have known how to adjust NOI dosing regimen depending on a specific need. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 6, 7, 10, 12, 13 are newly rejected under 35 U.S.C. 103(a) as obvious over *Billaut-Mulot et al.* (Vaccine 2001;19:95-102), in view of *Janeway et al.*

(Immunobiology c2001) as applied to claims 1-3, 5, 8, 9, 11, 14, 18-20, 26, 27 above, further in view of *Doria-Rose et al* (Methods 2003;31:207-16).

The combined teachings of *Billaut-Mulot* in view of *Janeway* do not detail other dosing regimen and route of administration as recited in these claims.

Doria-Rose supplemented the deficiency by establishing the general state of the art pertaining to combined vaccination of nucleic acids and protein antigens. *Doria-Rose* outlines the general state of the art pertaining to DNA vaccine strategies, including plasmid design, route of administration, and dosing regimens (see for example the abstract). *Doria-Rose* teaches the number of doses affects the immune response. A very immunogenic gene may require only a single dose, as was found for influenza HA, whereas in most cases, more than one immunization is required (§ 11, page 210). *Doria-Rose* teaches for many antigens, 1μg is all that is required by a gene gun delivery (a particle acceleration device, e.g. 2nd paragraph, page 211). *Doria-Rose* teaches the timing of doses also affects the outcome of vaccination. Using recombinant HIV-1 gp120 as an example, *Doria-Rose* teaches a resting period of approximately 20 weeks between the second and third immunizations resulted in significant, often 10-fold or more increases in antibody production. *Doria-Rose* names the process as prime-boost or combination immunization, and states, "GENERALLY, THE REGIMEN BEGIN WITH ONE OR MORE DOSES OF THE FIRST VACCINE-"PRIME"-FOLLOWED BY ONE OR MORE DOSES OF THE SECOND MODALITY-"BOOST". THE FIRST MAJOR STUDY TO USE THIS APPROACH FOR SIV SHOWED STERILIZING IMMUNITY ELICITED BY PRIMING WITH A RECOMBINANT VACCINIA VIRUS THAT ENCODED SIV ENVELOPE PROTEIN AND BOOSTING WITH PURIFIED ENVELOPE PROTEIN"

(paragraph bridging columns 1 & 2, page 212). *Doria-Rose* goes on to teach, "IN MANY CASES, A COMBINATION OF TWO MODALITIES ELICITS BETTER IMMUNE RESPONSES THAN EITHER VACCINE ALONE". In table I, *Doria-Rose* lists successful DNA prime-boost vaccines in animal models including influenza vaccine using a combination of DNA plasmid and modified vaccinia Ankara. *Doria-Rose* also teaches the advantage of using antigen combinations in a DNA vector construct because different antigens are likely to be targets of antibody and cellular responses, and could cover the unique individual CTL responses, and antigen variations due to viral mutation (§ 5, page 208).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the DNA-prime and protein-boost strategy as taught by *Doria-Rose* in developing the vaccine as taught by *Billaut-Mulot* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it is likely to generate better immune response as suggested by *Doria-Rose*. Given the knowledge of the skilled as illustrated by *Billaut-Mulot* in view of *Janeway* and *Doria-Rose*, the limitations fall within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

The applicant argues the difference in administration intervals between *Doria-Rose* and the claimed invention is not trivial as the examples of the present invention show an enhanced immune response when compared clustered administration and conventional administration.

In response, the original rejection of *Doria-Rose* has been revised in view of the claim amendment. As to the so-called "conventional administration". A closer look of the specification, it refers to a "pulse" administration as described e.g. in page 79 of the specification, wherein the differences are 0, 2, 4 days apart for clustered administration, and 0 and 4 days apart for the conventional pulse administration. The specification fails to compare the interval between 2-6 days and 7-14 days. Accordingly, in view of the teaches of *Billaut-Mulot et al.* in view of *Janeway et al.* and in the absence of evidence to the contrary, the limitation falls within bounds of optimization.

Claim 21 is newly rejected under 35 U.S.C. 103(a) as obvious over *Billaut-Mulot et al.* (Vaccine 2001;19:95-102), in view of *Janeway et al.* (Immunobiology c2001) as applied to claims 1-3, 5, 8, 9, 11, 14, 18-20, 26, 27 above, further in view of *Berglund et al* (Vaccine 1999;17:497-507), and *Horvath et al* (Immunol Lett 1998;60:127-36).

The combined teachings of *Billaut-Mulot* in view of *Janeway* as detailed *supra* differ from instant claim in that they did not specifically mention using the DNA prime and protein boost regimen for influenza virus, or using multiple influenza antigens.

Berglund supplemented the combined teachings by establishing it was well known in the art in the context of developing influenza vaccine that one could express more than one antigen of influenza virus in a vector, using multiple dosing regimen and different routes of administration. *Berglund* teaches a method of eliciting a T cell response against influenza viral infection in a mammalian host, the method comprises intranasal, intravenous, subcutaneous or intramuscular administering a pharmaceutical

composition comprising a recombinant SFV vector particles encoding and expressing HA or NP, or HA & NP antigens to C57B1/6 or Balb/c mice, followed by a booster dose in half of the mice at day 14 after the initial prime dose (e.g. § 3.1, page 499, fig. 3, 11, § 3.4).

Horvath supplemented the combined teachings by establishing it was well known in the art that recombinant HA peptide is capable of inducing T cell responses that protect mice against influenza virus infection (e.g. the abstract and figures).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the DNA-prime and protein-boost strategy as taught by *Billaut-Mulot* in view of *Janeway* in developing influenza vaccine. The ordinary skilled artisan would have been motivated to modify the claimed invention because it is likely to generate better immune response as suggested by *Billaut-Mulot*. Given the success as taught by *Billaut-Mulot, Berglund* and *Horvath*, one would have had a reasonable expectation of success applying NOI-protein vaccine regimen for influenza. Although none of the cited references states exact timing between the DNA-priming and protein-boost for influenza virus vaccine, given the knowledge of the skilled as illustrated by *Billaut-Mulot* in view of *Janeway*, such timing could be established through routine experimentation, and hence the limitation fall within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7:30 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
March 5, 2009